MODULE 1.3.1.1 PROPOSED PROFESSIONAL INFORMATION FOR

Desvenlafaxine 50 mg and 100 mg (EXTENDED RELEASE-TABLETS)

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DEPVEN 50 XL, 50 mg extended release tablets.

DEPVEN 100 XL, 100 mg extended release tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DEPVEN 50 XL: Each extended release tablet contains desvenlafaxine succinate equivalent to desvenlafaxine 50 mg.

DEPVEN 100 XL: Each extended release tablet contains desvenlafaxine succinate equivalent to desvenlafaxine 100 mg.

For the full list of excipients, **see Section 6.1**.

3. PHARMACEUTICAL FORM

Film coated, extended release tablets.

DEPVEN 50 XL, 50 mg extended release tablets are light pink coloured, round, biconvex, film coated tablets, debossed with ‘50’ on one side and plain on other side.

DEPVEN 100 XL, 100 mg extended release tablets are dark brown to red coloured, round, biconvex, film coated tablets, debossed with ‘100’ on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DEPVEN XL extended release tablets are indicated for the treatment of major depressive disorder (MDD).

4.2 Posology and method of administration

Posology:

The recommended adult dose of DEPVEN XL for the treatment of major depressive disorder is 50 mg daily, with or without food, with a maximum dose of 100 mg daily. The dose should be increased gradually and should be at an interval of not less than 7 days.

Special populations

Renal Impairment:

The recommended starting dose of DEPVEN XL in patients with severe renal impairment (24-hr CrCl < 30 mL/min) or end-stage renal disease (ESRD) is 50 mg every other day.

Because the clearance may vary in these patients, individualisation of dosage may be ideal. Supplemental doses should not be given to patients after dialysis **(see section 5.2).**

Hepatic Impairment:

No dosage adjustment of DEPVEN XL is necessary for patients with hepatic impairment **(see section 5.2).**

Use in elderly patients:

No dosage adjustment is required solely on the basis of age; however, possible reduced renal clearance of DEPVEN XL should be considered when determining dose (**see section 5.2**).

Paediatric use:

Safety and efficacy in patients less than 18 years of age has not been established.

Discontinuing DEPVEN XL:

Symptoms associated with the discontinuation of serotonin-norepinephrine reuptake inhibitors (SNRI's) and selective serotonin reuptake inhibitors (SSRI's) may occur when discontinuing DEPVEN. It is recommended that the dose be gradually reduced instead of abruptly stopping treatment.

If intolerable symptoms occur following a dose reduction or upon discontinuation of treatment, resuming the previously prescribed dose may be considered. Subsequently, the medical practitioner may continue decreasing the dose but at a more gradual rate.

Switching patients from other anti-depressants to DEPVEN XL:

Discontinuation symptoms may occur when switching patients from other antidepressants, including venlafaxine, to DEPVEN XL. Tapering of the initial

dose may be necessary to minimise discontinuation symptoms.

Method of administration:

DEPVEN XL is for oral administration and should be swallowed whole.

4.3 Contraindications

DEPVEN XL is contraindicated:

- In patients with known hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or any of the excipients of DEPVEN XL **(see section 6.1).**
- In patients using monoamine oxidase inhibitors (MAOIs) or within at least 14 days of discontinuing treatment with a MAOI. At least 7 days should be allowed after stopping DEPVEN XL before starting a MAOI. Severe adverse reactions may occur when therapy is initiated with serotonin-norepinephrine reuptake inhibitors (SNRI's) and/or selective serotonin

reuptake inhibitors (SSRI's) such as DEPVEN XL soon after discontinuation of a MAOI and when a MAOI is initiated soon after discontinuation of SSRI/SNRI medicines. These reactions include tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures and death. **(see section 4.4)**.

- In children less than 18 years of age as safety and efficacy has not been established **(see section 4.5).**
- In pregnancy and lactation **(see section 4.6).**

4.4 Special warnings and precautions for use

Clinical worsening of depressive symptoms, unusual changes in behaviour and suicidality:

Patients with major depressive disorder may experience worsening of their depression and/or suicidal ideation and behaviour, whether or not they are taking antidepressant medicines. This risk may persist until significant remission occurs. Although a causal role for antidepressant medicines in inducing such behaviour has not been established, patients being treated with DEPVEN XL should be observed closely for clinical worsening and suicidality, especially at the beginning of a course of therapy or when changes in dosage are made.

Due to the possibility of co-morbidity, the same precautions should be taken when treating patients with other psychiatric and non-psychiatric disorders.

Symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania and mania may occur in patients treated with antidepressants for major depressive disorder as well as other indications, both psychiatric and non-psychiatric. Although a causal link

between the emergence of suicidal impulses has not been established, changing the therapeutic regimen, including possibly discontinuing DEPVEN XL may be

considered in patients for whom such symptoms are severe, abrupt in onset,

or were not part of the patients presenting symptoms.

If a decision is made to discontinue treatment, DEPVEN XL should be tapered. **(see section 4.2)**

Screening patients for bipolar disorder:

Major depressive disorder may be the initial presentation of bipolar disorder. Treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Patients should therefore be adequately screened for the risk of bipolar disorder. Such screening should include a detailed psychiatric history, including family history of suicide, bipolar disorder and depression. DEPVEN XL is not

approved for treating bipolar disorder.

Mania/hypomania:

Mania/hypomania may occur in patients treated with DEPVEN XL therefore caution should be exercised in patients with a history or family history of mania or hypomania. **(see section 4.8)**

Serotonin syndrome:

The development of a potentially life-threatening serotonin syndrome may occur with DEPVEN XL treatment, particularly with concomitant use of other serotonergic medicines (such as SSRI's, SNRI's and triptans) and medicines that impair metabolism of serotonin (including (MAOI's). Serotonin syndrome symptoms may include mental state changes (such as agitation, hallucinations and coma), autonomic instability (e.g. tachycardia, labile blood pressure and hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (such as nausea, vomiting and diarrhoea). **(see section 4.8)**

The concomitant use of DEPVEN XL with serotonin precursors such as tryptophan supplements is not recommended.

All patients taking DEPVEN XL should be monitored for serotonin syndrome and it should be discontinued if symptoms occur.

Switching patients from a monoamine oxidase inhibitor (MAOI) intended to treat psychiatric disorders:

At least 14 days should lapse between discontinuation of a MAOI and initiation of therapy with DEPVEN XL. At least 7 days should be allowed after stopping

DEPVEN XL treatment before starting a MAOI.

Use of DEPVEN with other MAOI's such as linezolid or methylene blue:

Patients being treated with linezolid or intravenous methylene blue should not be started on DEPVEN XL as there is an increased risk of serotonin syndrome. In patients already being treated with DEPVEN XL, alternatives to linezolid or methylene blue should be considered.

Narrow-angle glaucoma:

Mydriasis may occur with DEPVEN XL treatment therefore patients with raised intraocular pressure or those at risk of developing acute narrow-angle glaucoma should be monitored. **(see section 4.8)**

Ischemic cardiac adverse events:

Cardiac adverse events such as myocardial ischemia, myocardial infarction, and coronary occlusion requiring revascularisation may occur in patients with underlying cardiac risk factors taking DEPVEN XL.

Discontinuation symptoms:

Adverse reactions that may occur with discontinuation of DEPVEN XL include dizziness, withdrawal syndrome, nausea and headache. Discontinuation symptoms occur more frequently with longer duration treatment. Abrupt discontinuation of DEPVEN XL may also have adverse effects such as dysphoric mood, irritability, agitation, sensory disturbances (e.g. paraesthiasis
such as electric shock sensations), anxiety, confusion, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. These events are generally self-limiting; however, serious discontinuation symptoms may occur. Patients should be monitored when discontinuing DEPVEN XL. A gradual dose reduction is recommended whenever possible. If intolerable symptoms occur after dose reduction or discontinuation of treatment, resuming the previously prescribed
dose may be considered.

Adverse reactions leading to discontinuation of therapy:

Adverse effects such as nausea, dizziness, headache and vomiting may lead to discontinuation of treatment with DEPVEN XL.

Adverse reactions reported with other SNRI's:

While gastrointestinal bleeding is not considered an adverse effect for DEPVEN XL, it is an adverse event for other SNRI's and therefore may occur with DEPVEN
XL.

Physical and psychological dependence:

DEPVEN XL has not been studied for its potential for abuse. However, similar medicines have shown no indication of dependence.

Co-administration with medicines containing venlafaxine:

DEPVEN XL (o-desmethylvenlafaxine) is the major active metabolite of venlafaxine, a medicine used to treat major depressive disorder, generalised anxiety, social anxiety and panic disorders. DEPVEN XL should not be used with medicines containing venlafaxine hydrochloride or other medicines containing the active ingredient of DEPVEN XL.

Increased blood pressure:

Increases of blood pressure may occur with DEPVEN XL treatment, especially in patients receiving higher doses. Pre-existing hypertension should be controlled before treatment with DEPVEN XL.

Patients receiving DEPVEN XL should have regular monitoring of blood pressure as increases requiring immediate treatment may occur. Sustained blood pressure increases could have adverse consequences therefore a dose reduction or discontinuation of DEPVEN XL should be considered in patients who experience a sustained increase in blood pressure.

Caution should be exercised when treating patients with underlying conditions which might be compromised by increased blood pressure. **(see section 4.8)**

Cardiovascular/Cerebrovascular:

Caution should be exercised when administering DEPVEN XL to patients with cardiovascular, cerebrovascular or lipid metabolism disorders due to potential to increases in blood pressure and heart rate.

Serum lipids:

Dose-related elevations in fasting serum total cholesterol, low density lipoprotein (LDL) cholesterol, and triglycerides may occur with DEPVEN XL treatment. Measurement of serum lipids should be considered during treatment with DEPVEN XL.

Seizures:

Seizures may occur in patients taking DEPVEN XL. Caution should therefore be taken when prescribing DEPVEN XL to patients with seizure disorder.

Abnormal bleeding:

Medicines that inhibit serotonin reuptake may lead to abnormalities of platelet aggregation. Concomitant use of aspirin, nonsteroidal anti-inflammatory medicines, warfarin and other anticoagulants with DEPVEN XL may add to the risk of bleeding. Bleeding related adverse events related to SSRI's and SNRI's may range from ecchymosis, hematoma, epistaxis, and petechiae to life threatening haemorrhages. DEPVEN XL should be used cautiously in patients predisposed to bleeding.

Hyponatraemia:

Hyponatraemia and/or the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion may occur with SSRI's and SSRI's, including DEPVEN XL, usually in volume depleted or dehydrated patients (including elderly patients taking diuretics). **(see section 4.8)**

Interstitial lung disease and eosinophilic pneumonia:

Interstitial lung disease and eosinophilic pneumonia associated with venlafaxine (which desvenlafaxine is an active metabolite of) may occur with DEPVEN XL use. The possibility of these adverse events should be considered in patients being treated with DEPVEN XL who present with dyspnoea, cough or chest discomfort. Discontinuation of DEPVEN XL may be considered.

Use in elderly:

No dosage adjustment is required solely on the basis of age; however, possible reduced clearance of DEPVEN XL should be considered when determining dose. There may be an increased incidence of orthostatic hypotension in patients ≥ 65 years of age treated with DEPVEN XL.

Increases in systolic blood pressure may be more prevalent in patients ≥ 65 years of age treated with DEPVEN XL.

Paediatric population:

Safety and efficacy in children under 18 years of age has not been established. **(see section 4.4)**

4.5 Interaction with other medicines and other forms of interaction

List of medicines that interact with DEPVEN XL:

Monoamine oxidase inhibitors (MAOI)

Serious adverse effects may occur in patients who have been recently discontinued from a monoamine oxidase inhibitor (MAOI) and started on antidepressants with pharmacological properties such as DEPVEN XL (SSRI's and SNRI's), or patients who have recently had SSRI or SNRI therapy

discontinued prior to initiation of a MAOI. These adverse effects include tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures and death. Concomitant use of DEPVEN XL with MAOI's is contraindicated. **(see section 4.3 and 4.4)**

Central nervous system (CNS)-active medicines:

Caution should be exercised when combining DEPVEN XL with other CNS-active medicine as safety has not been evaluated.

Medicines that affect the serotonergic neurotransmitter system:

Serotonin syndrome, a potentially life-threatening condition may occur with DEPVEN XL treatment, particularly when combined with other medicines that affect the serotonergic neurotransmitter system (including triptans, SSRI's, other

SNRI's, lithium, sibutramine, tramadol, St. Johns' wort *(hypericum perforatum),* pethidine), with medicines that impair metabolism of serotonin (such as MAOI's,

including linezolid, an antibiotic which is a reversible non-selective MAOI), or with serotonin precursors (such as tryptophan supplements). Serotonin syndrome may manifest as mental changes, autonomic instability, neuromuscular aberrations and/or gastrointestinal symptoms.

Ethanol:

Patients taking DEPVEN XL should be advised to avoid alcohol consumption.

Medicines that interfere with haemostasis:

The concomitant use of DEPVEN XL with antiplatelet or anticoagulant medicines such as nonsteroidal anti-inflammatory medicines and warfarin may increase the risk of bleeding.

CYP3A4 inhibitors:

CYP3A4 is involved in the elimination of DEPVEN XL. Concomitant use of DEPVEN XL with medicines which are potent inhibitors of CYP3A4 may result in

increased exposure to DEPVEN XL.

Inhibitors of other CYP enzymes:

Medicines which inhibit CYP isozymes 1A1, 1A2, 2A6, 2D6, 2C8, 2C9, 2C19 and 2E1 are not expected to have a significant impact on the pharmacokinetic profile of DEPVEN XL.

Medicines metabolised by CYP2D6:

DEPVEN XL is a weak inhibitor of CYP2D6 at a dose of 100 mg daily. Concomitant use of DEPVEN XL with medicines metabolised by CYP2D6 such as

desipramine, atomoxetine, dextromethorphan, metoprolol, nebivolol perphenazine and tolterodine may result in increased concentrations of that medicine and decreased concentrations of its CYP2D6 metabolites.

Medicines metabolised by CYP3A4:

Concomitant use of DEPVEN XL with a medicine metabolised by CYP3A4, such as midazolam may result in decreased exposure to that medicine.

Medicines metabolised by a combination of both CYP2D6 and CYP3A4:

DEPVEN XL does not have a clinically relevant effect on medicines such as tamoxifen and aripiprazole which are metabolised by a combination of both CYP2D6 and CYP3A4 enzymes.

Medicines metabolised by CYP1A2, 2A6, 2C8, 2C9, and 2C19:

DEPVEN XL does not inhibit CYP1A2, 2A6, 2C8, 2C9, and 2C19 isozymes and would not be expected to affect the pharmacokinetic profile of medicines metabolised by them.

P-glycoprotein transporter:

DEPVEN XL is not a substrate nor inhibitor of P-glycoprotein transporter.

Laboratory test interactions:

False-positive urine immunoassay screening tests for phencyclidine (PCP) and amphetamine may occur in patients taking DEPVEN XL. This is due to the lack of specificity of the screening tests. These false positive results may occur for several days after discontinuation of DEPVEN XL. Confirmatory tests such as gas chromatography or mass spectrometry will distinguish DEPVEN XL from PCP and amphetamine.

Electroconvulsive therapy:

There are no data on the risks or benefits of electroconvulsive therapy combined with DEPVEN treatment for MDD.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of DEPVEN XL in pregnancy has not been established. If DEPVEN XL is used until, or shortly before birth, discontinuation symptoms may occur in the newborn.

Complications such as the need for respiratory support, tube feeding, or prolonged hospitalisation may occur in neonates exposed to SNRI's or SSRI's late in the third trimester. Such complications can arise immediately upon delivery. Patients should therefore be advised to notify their doctor if they become pregnant or intend to become pregnant during therapy.

Lactation:

DEPVEN XL (o-desmethylvenlafaxine) is secreted in human milk. Due to the potential of serious adverse effects in breastfed infants from DEPVEN XL, a decision should be made whether to discontinue breastfeeding or discontinue DEPVEN XL taking into account the importance of the medicine to the mother.

Fertility:

The effect on fertility has not been established.

4.7 Effects on ability to drive and use machines

Since DEPVEN XL is a CNS-active medicine, it may impair judgement, thinking and motor skills. Patients should therefore be cautioned about their ability to drive or operate machinery while taking DEPVEN XL.

4.8 Undesirable effects

Summary of side effect profile:

The most common adverse events associated with DEPVEN XL include nausea, dry mouth, constipation, dizziness, headache, insomnia and hyperhidrosis.

Tabulated list of adverse reactions:

The following adverse reactions have been classified in the following way: "Frequent, less frequent and frequency not known".

System organ class	Undesirable effects
Immune system disorders	**Less frequent:** Hypersensitivity.
Metabolism and nutrition disorders	**Frequent:** Decreased appetite. **Less frequent:** Hyponatraemia.
Psychiatric disorders	**Frequent:** Insomnia, anxiety, abnormal dreams, nervousness, decreased libido, anorgasmia. **Less frequent:** Withdrawal syndrome, abnormal orgasm, depersonalisation,

	hypomania, hallucinations.
Nervous system disorders	**Frequent**: Dizziness, headache, somnolence, tremor, paraesthesia, dysgeusia, disturbance in attention, vertigo. **Less frequent:** Syncope, convulsion, dystonia.
Eye disorders	**Frequent:** Blurred vision, mydriasis.
Ear and labyrinth disorders	**Frequent:** Tinnitus, vertigo
Cardiac disorders	**Frequent:** Palpitations, tachycardia, increased blood pressure.
Vascular disorders	**Frequent:** Hot flush. **Less frequent:** Orthostatic hypotension, peripheral coldness.
Respiratory, thoracic and mediastinal disorders	**Frequent:** Yawning. **Less frequent:** Epistaxis.
Gastrointestinal disorders	**Frequent:** Nausea, dry mouth, constipation, diarrhoea, vomiting.
Skin and subcutaneous tissue disorders	**Frequent:** Hyperhidrosis, rash. **Less frequent:** Alopecia, photosensitivity reaction, angioedema Steven Johnson syndrome.

Musculoskeletal and connective tissue disorders	**Frequent:** Musculoskeletal stiffness**.**
Renal and urinary disorders	**Less frequent:** Urinary hesitation, proteinuria, urinary retention.
Reproductive system and breast disorders	**Frequent:** Erectile dysfunction, delayed ejaculation, ejaculation failure. **Less frequent:** Ejaculation disorder, sexual dysfunction.
General disorders and administration site conditions	**Frequent:** Fatigue, chills, asthenia, feeling jittery, irritability.
Investigations	**Frequent:** Increased weight, increased blood pressure, decreased weight. **Less frequent:** Increased blood cholesterol, increased blood triglycerides, abnormal liver function test, increased blood prolactin.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the 6.04 Adverse Drug Reaction Reporting Form, found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8 or to Cipla Medpro (Pty) Ltd (by e-mail: drugsafetysa@cipla.com).

4.9 Overdose

There is limited clinical experience with DEPVEN XL overdosage in humans.

No specific antidotes for DEPVEN XL are known. Induction of emesis is not recommended. Because of the moderate volume of distribution of this medicine, forced diuresis, dialysis, haemoperfusion, and exchange transfusion are unlikely to be of benefit.

Treatment should consist of general measures taken when managing overdose with an SSRI/SNRI. Adequate airway, oxygenation and ventilation should be ensured. Cardiac rhythm and vital signs should be monitored. General supportive and symptomatic measures are recommended. Activated charcoal should be administered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification:

A 1.2 Psycoanaleptics (antidepressants)

Mechanism of action:

Desvenlafaxine is the major active metabolite of venlafaxine which is also approved for treatment of depression. Preclinical studies have shown that it is a selective serotonin and norepinephrine reuptake inhibitor. The clinical efficacy is

thought to be related to the potentiation of these neurotransmitters in the central nervous system.

Desvenlafaxine lacks significant affinity for numerous receptors, including muscarinic-cholinergic, H_1-histaminergic, or α_1-adrenergic receptors. Desvenlafaxine also lacks affinity for various ion channels, including calcium, chloride, potassium and sodium ion channels, as well as monoamine oxidase (MAO) inhibitory activity.

5.2 Pharmacokinetic properties

Absorption:

Desvenlafaxine is well absorbed. The absolute oral bioavailability of desvenlafaxine is 80 %. The mean time to peak plasma concentrations (t_{max}) is about 7,5 hours after oral administration. Following a 100 mg single dose, the predicted AUC and C_{max} are 6,747 ng.hr/ mL and 376 ng/ mL, respectively. There is a linear increase in AUC and C_{max} after administration of 50 mg to 600 mg doses.

Food effect:

There is an increase in C_{max} of desvenlafaxine under fed conditions (high-fat meal) while desvenlafaxine exposure was not significantly affected by food. This difference is not clinically significant; therefore, desvenlafaxine can be taken without regard to meals.

Distribution:

With once-daily dosing, steady-state plasma concentrations are achieved within approximately 4-5 days.

The plasma protein binding of desvenlafaxine is low (30 %) and is not dependent on medicine concentration. Desvenlafaxine's volume of distribution at steady state following intravenous administration is 3,4 L/Kg, indicating distribution into non-vascular compartments.

Biotransformation:

Desvenlafaxine is primarily metabolised by conjugation (mediated UGT isoforms, including UGT1A1, UGT 1A3, UGT2B4, UGT2B15, and UGT2B17) and to a minor extent through oxidative metabolism. CYP3A4 is the predominant cytochrome P450 isozyme mediating the oxidative metabolism (N-demethylation) of desvenlafaxine.

Elimination:

The terminal elimination half-life of desvenlafaxine is approximately 11 hours.

Approximately 45 % of desvenlafaxine is excreted unchanged in the urine. Approximately 19 % of the administered dose is excreted as the glucuronide metabolite and < 5 % as the oxidative metabolite in urine.

Special populations:

Renal impairment:

The total body clearance of desvenlafaxine is reduced by 29 % in patients with mild renal impairment, 39 % in patients with moderate renal impairment, and by 51 % in patients with severe renal impairment. Patients with end stage renal disease (ESRD) have a 58 % reduction in total body clearance of desvenlafaxine. This reduced clearance results in increases in AUC's of 42 % in mild renal impairment, 56 % in moderate renal impairment, 108 % in severe renal

impairment and 116 % is ESRD patients. The mean terminal half-life is prolonged to 13,5, 15,5, 17,6, and 22,8 hours in mild, moderate, severe renal impairment and ESRD respectively as compared to 11,1 hours in healthy patients. Less than 5 % of the medicine in the body is cleared during a standard 4-hour haemodialysis procedure. Supplemental doses of DEPVEN should therefore not be given to patients after dialysis. Dosage adjustment is recommended in patients with significant renal function impairment. **(see section 4.2)**

Hepatic impairment.

The AUC of desvenlafaxine is increased by approximately 31 % and 35 % in patients with moderate and severe hepatic impairment respectively. Patients with

mild hepatic impairment however, have comparable AUC values to healthy patients.

The mean half-life is increased to approximately 13 and 14 hours in moderate and severe hepatic impairment respectively.

Paediatric population:

Safety and efficacy in patients less than 18 years of age has not been established.

Elderly:

In a trial of healthy subjects administered doses of up to 300 mg, there was an age-dependent decrease in desvenlafaxine clearance, resulting in a 32 %

increase in C_{max} and 55 % increase in AUC values in subjects greater than 75 years of age, as compared with subjects 18 to 45 years of age.

No dosage adjustment is required solely on the basis of age; however, possible reduced renal clearance of desvenlafaxine should be considered when determining dose (**see section 4.2**).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Hypromellose (Benecel K100M PHARM CR)
- Hypromellose (Methocel K100LV CR)
- Magnesium stearate

- Microcrystalline cellulose (Comprecel M 101)
- Povidone K-90
- Purified water
- Talc
- Opadry Pink 03F84770 (for 50 mg formulation)
- Opadry Brown 03F86990 (for 100 mg formulation)

Contents of the film-coating:

Opadry Pink 03F84770

- HPMC 2910/Hypromellose (6cP)
- Iron oxide red.
- Macrogol/ PEG 6000
- Talc
- Titanium dioxide

Opadry Brown 03F86990

- HPMC 2910/Hypromellose (6cP)
- Iron oxide black
- Iron oxide red.
- Macrogol/ PEG 4000
- Titanium dioxide

6.2 Incompatibilities

NOT APPLICABLE

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 30 °C in the original container to protect from moisture.

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

DEPVEN XL Extended Release Tablets are packed in Blister and HPDE bottle pack(s). Such blisters and/or HDPE bottles are further packed in a Carton along with Pack Insert.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD

Building 9, Parc du Cap,

Mispel Street,

Belville, 7530,

RSA

Company Contact Details:

Phone: +27 21 943 4200

Customer Care: 080 222 6662

E-mail: info@cipla.com

8. REGISTRATION NUMBER

DEPVEN 50 XL: 53/1.2/0048
DEPVEN 100 XL: 53/1.2/0049

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 June 2021

10. DATE OF REVISION OF THE TEXT

N/A